AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 129, No. 3
Printed in U.S.A.

ESTROGEN AND ANDROGEN LEVELS IN WOMEN TREATED WITH RADIATION FOR CERVICAL CANCER—POSSIBLE INFLUENCE ON BREAST CANCER RISK

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Eby, N. L. (Pittsburgh Cancer Institute, Pittsburgh, PA 15213), J. D. Boice, Jr., E. B. Gold, R. N. Hoover, and D. L. Loriaux. Estrogen and androgen levels in women treated with radiation for cervical cancer—possible influence on breast cancer risk. *Am J Epidemiol* 1989;129:527–32.

In 1984–1985, estrogen and androgen levels in blood sera were measured in 320 women who had been treated for cervical cancer in the early 1960s. Study subjects were from US clinics in Baltimore, Maryland; Boston and Norfolk, Massachusetts; Buffalo, New York; Houston, Texas; and San Juan, Puerto Rico. These clinics had participated in a larger international follow-up study of cervical cancer in which a 20–30% reduction in breast cancer risk was linked to prior pelvic irradiation, even when treatment occurred after menopause. Overall, the 203 irradiated and 117 nonirradiated women had similar mean levels of estradiol, estrone, androstenedione, and testosterone. However, there appeared to be negative, albeit inconsistent, trends for androstenedione, testosterone, and estrone, suggesting that the irradiated women had lower levels of these hormones when compared with the nonirradiated women. These differences did not reach the level of statistical significance. While chance could partially explain these findings, it is plausible that the frequently observed protective association of breast cancer with pelvic irradiation could be due in part to a decrease in steroid hormones that is secondary, perhaps, to adrenal irradiation.

androgens; breast neoplasms; estrogens; ovariectomy; radiotherapy

Both pelvic irradiation and bilateral oophorectomy have been associated with reduced risk of breast cancer, but they appear to differ in the extent of the protection they confer. Several studies of cervical cancer patients (1, 2) have reported a greater

Received for publication July 29, 1987, and in final form June 10, 1988.

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This paper is based on a thesis submitted by Nancy L. Eby to The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD, in partial fulfillment of the requirements for the Ph.D. degree.

Supported in part by a training grant from the National Cancer Institute.

The authors thank Dan Ames, Westat Inc., for his assistance in data collection, and the following clinical collaborators for their assistance in recruiting patients for this study: Dr. Antonio Bosch, I. G. Martinez Oncology Hospital, San Juan, Puerto Rico; Dr. Diane Cookfair, Roswell Park Memorial Institute, Buffalo, NY; Dr. Ralph Freedman, M. D. Anderson Hospital, Houston, TX; Dr. Leroy Parker, Southwood Community Hospital, Norfolk, MA; Dr. George Richardson, Massachusetts General Hospital, Boston, MA; and Dr. Robert Slawson, University of Maryland Hospital, Baltimore, MD. In addition, the authors thank Dr. Howard Zacur, The Johns Hopkins Hospital, Baltimore, MD, for his advice concerning this study, and Joyce O'Leary for her technical assistance with the manuscript.

reduction in subsequent breast cancer risk in women who received pelvic radiotherapy than in nonirradiated women treated with surgery, which usually included bilateral oophorectomy. Irradiated women in a large international study of cervical cancer (1) experienced a statistically significant lower risk of breast cancer than did nonirradiated women of similar age at the time of treatment (irradiated: observed/expected = 0.70, 95 per cent confidence interval (CI): 0.6–0.8; nonirradiated: observed/expected = 0.95, 95 per cent CI: 0.8–1.1). This lower risk of breast cancer was also evident among cervical cancer patients irradiated after menopause when the castrating effect of high-dose radiation would be expected to be minimal, i.e., when most ovarian activity has already ceased. In contrast, among nonirradiated patients with cervical cancer, only those who received surgical treatment before menopause appeared to have a lower risk of breast cancer than the general population; this finding is similar to the protection associated with bilateral oophorectomy in women without cervical cancer (3–6).

These differences in breast cancer risk may arise from differing hormone profiles (7) between irradiated and nonirradiated patients. The purpose of this study was to determine whether irradiated cervical cancer cases differed from nonirradiated cervical cancer cases in serum levels of two estrogens, estradiol and estrone, and two androgens, testosterone and androstenedione.

Materials and methods

In 1984–1985, we conducted a cross-sectional study of serum hormone levels in a cohort of cervical cancer patients either treated with or not treated with radiation primarily in the early 1960s (range, 1943–1966). The study was conducted at US clinics in Baltimore, Maryland; Boston and Norfolk, Massachusetts; Buffalo, New York; Houston, Texas; and San Juan, Puerto Rico, that participated in a larger (31-clinic) international cohort study (n = 7,012) of late effects associated with radiation for cervical cancer (8, 9). Of the 2,665 survivors in this cohort, eligible subjects had responded to a mail questionnaire in 1982–1984, were living in the geographic area surrounding one of the six clinics, and had a telephone number available to facilitate patient contact and examination scheduling (n = 503). Of the 503 eligible patients, 76 were too ill to participate. Of the remaining 427 patients, 320 (75 per cent) participated, and 107 refused. The participation rates in the two treatment groups were similar.

Study participants were asked to come to their clinic of record, to complete a questionnaire on factors that might influence hormone levels, and to give a 30 cc blood sample. Information regarding breast cancer risk factors and cervical cancer treatment had already been collected as part of the larger cohort study. Serum levels of estradiol, estrone, androstenedione, and testosterone were determined by radioimmunoassay (10–13) at Hazleton Laboratories, Vienna, VA.

Analyses evaluated differences between the two treatment groups by using hormone levels as continuous and categorical outcome variables. For the categorical analyses, levels of the four hormones were divided into quartiles based on the overall distribution of the individual hormone values in the study population. Odds ratios were calculated comparing irradiated with nonirradiated subjects and using the lowest hormone quartile as the referent group.

A number of stratified analyses were performed to evaluate the effect of breast cancer risk factors and demographic factors on the relation between radiation treatment and hormone levels. Significance of trends was tested utilizing the Mantel-Haenszel chi statistic (14). To control confounding variables and test for effect modification in the categorical analyses, we used a polychotomous logistic regression model (15).

Table 1 characterizes irradiated and nonirradiated women by a number of potentially confounding variables. Of these vari-

TABLE 1

Distribution of irradiated and nonirradiated cervical cancer cases by selected demographic, treatment, and reproductive characteristics, US clinics, 1984–1985

	Irradiated (n = 203)		Nonirradiated (n = 117)		χ^2	df*	p value
	n	%	n	%			
Year of birth							
<1910	52	25	9	8			
1910–1919	81	40	41	35			
1920–1929	54	27	52	44			
≥1930	16	8	15	13			
					21.97	3	0.001
Age (years) at cervical diagnosis							
25–39	72	35	61	52			
40–44	41	20	22	19			
45–49	36	18	16	14			
50–70	54	27	18	15			
					9.94	3	0.02
Ovarian status							
Intact	150	74	15	13			
Unilateral oophorectomy	13	6	13	11			
Bilateral oophorectomy	37	18	88	75			
Oophorectomy, NOS†	3	2	1	1			
					117.65	3	0.001
Prior exogenous hormone use							
Yes	20	10	25	21			
No	178	88	88	75			
Unknown	5	2	4	3			
					8.63	2	0.01
Smoking habits							
Ever smoked	70	34	66	56			
Never smoked	129	64	51	44			
Unknown	4	2	0				
					15.96	2	0.001
Quetelet index (weight/height^2 × 1,000)							
<25	89	44	53	45			
≥25	112	55	64	55			
Unknown	2	1	0				
					1.19	2	0.55

* df, degrees of freedom.

† NOS, not otherwise specified.

ables, only year of birth appeared to confound the results for all four hormones, and prior exogenous hormone use confounded the results for estradiol.

Nonparticipants were slightly older than participants, and this difference was seen in both treatment groups.

RESULTS

The hormone data were analyzed as continuous and categorical variables. Both analyses yielded similar results. Irradiated and nonirradiated women had similar mean levels of the four hormones (table 2) when adjusted for confounding factors. The distributions of the hormone data in the continuous and categorical analyses showed negative, albeit inconsistent, trends for androstenedione, testosterone, and estrone, suggesting that irradiated women had lower levels of these hormones than did nonirradiated women (table 3). However, these trends were not statistically significant, and no trend was seen for estradiol levels.

TABLE 2

Adjusted mean hormone levels (pg/ml) for irradiated and nonirradiated subjects, US clinics, 1984–1985

	n	Adjusted means ± SE*	*p* value†
Androstenedione			
Irradiated	200	504.6 ± 21.4	0.93
Nonirradiated	112	501.4 ± 27.8	
Unknown	8		
Testosterone			
Irradiated	184	182.0 ± 7.1	0.16
Nonirradiated	103	198.8 ± 9.3	
Unknown	33		
Estradiol			
Irradiated	192	11.7 ± 1.0	0.70
Nonirradiated	108	11.2 ± 1.1	
Unknown	20		
Estrone			
Irradiated	197	45.9 ± 3.1	0.41
Nonirradiated	111	50.2 ± 4.0	
Unknown	12		

* SE, standard error.

† *p* value for test of difference between means adjusted for year of birth. Estradiol levels were also adjusted for history of prior use of exogenous hormones.

To evaluate the effect of radiotherapy independent of ovarian status, we calculated the quartile-specific odds ratios of each hormone among irradiated and nonirradiated women who had bilateral oophorectomies (table 3). Negative trends stronger than those observed for the total study population were seen in levels of androstenedione, testosterone, and estrone. However, only the trend for androstenedione was statistically significant. Once again, there was no evidence of a trend in estradiol levels. Unfortunately, there were insufficient numbers of nonirradiated women with ovaries intact for meaningful evaluation of this group separately.

It was of interest to evaluate hormone levels in women who were treated after menopause. Because the majority of nonirradiated women treated after menopause had bilateral oophorectomies, the analysis was limited to women who had had both ovaries removed. In addition, hormone levels had to be divided into high and low categories instead of quartiles to provide more stable estimates. Irradiated, postmenopausal women who had had their ovaries removed had lower levels of both androgens and both estrogens than did nonirradiated, postmenopausal women of similar ovarian status. Again, only the odds ratio for androstenedione was statistically significant.

DISCUSSION

The aim of this study was to determine what factors may have provided irradiated cervical cancer cases with greater protection against breast cancer than was seen in their nonirradiated counterparts. We chose to explore a hormonal hypothesis since many breast cancer risk factors point to a hormonal etiology. None of the differences in hormone levels between the two treatment groups reached a level of statistical significance. Although the mean levels of the hormones were similar, the distributions of androstenedione, testosterone, and estrone levels were slightly, but consistently, lower in irradiated women than in nonirradiated women, suggesting that hormonal differences may exist.

The strongest evidence suggesting a possible radiation effect was the lower levels of androstenedione, testosterone, and estrone levels in irradiated women who had had oophorectomies and the lower levels of all four hormones in the subset of this group who were menopausal at treatment. The results in the oophorectomized and menopausal women were based on small numbers and were not statistically significant. However, we find the suggestion of lower hormone levels in these subsets of irradiated women to be interesting. Differences in hormone levels would not be expected between irradiated and nonirradiated women without ovaries. Similarly, if the protection against breast cancer was due to the effect of radiation on ovarian hormonal production, irradiated, postmenopausal women without ovaries would not be expected to be protected. Thus, the trend toward lower hormone levels in these irradiated women suggests that radiotherapy may have affected adrenal hormone pro-

TABLE 3

Adjusted odds ratios for irradiated compared with nonirradiated women by hormone quartile, US clinics, 1984–1985

	Total population		Women without ovaries	
	Adjusted odds ratio*	95% confidence interval	Adjusted odds ratio*	95% confidence interval
Androstenedione (pg/ml)				
<282	1.00		1.00	
282–432	1.20	0.57–2.56	0.61	0.21–1.80
433–621	0.90	0.43–1.86	0.42	0.13–1.37
≥622	0.82	0.40–1.70	0.43	0.15–1.23
	(χ trend = −0.74, p = 0.23)†		(χ trend = −1.65, p = 0.05)†	
Testosterone (pg/ml)				
<128	1.00		1.00	
128–171	1.28	0.57–2.87	1.14	0.36–3.62
172–223	0.53	0.26–1.11	0.73	0.24–2.16
≥224	0.79	0.36–1.71	0.46	0.12–1.70
	(χ trend = −1.51, p = 0.07)†		(χ trend = −1.30, p = 0.10)†	
Estradiol (pg/ml)				
<4.1	1.00		1.00	
4.1–5.6	0.71	0.32–1.55	1.35	0.37–4.87
5.7–9.5	0.75	0.36–1.58	0.90	0.26–3.13
≥9.6	1.15	0.51–2.62	1.61	0.44–5.82
	(χ trend = 0.33, p = 0.37)†		(χ trend = 0.40, p = 0.34)†	
Estrone (pg/ml)				
<26.6	1.00		1.00	
26.6–36.9	0.93	0.44–1.94	0.73	0.23–2.32
37.0–52.9	0.89	0.42–1.86	0.63	0.20–7.98
≥53.0	0.65	0.31–1.34	0.61	0.19–1.91
	(χ trend = −1.25, p = 0.11)†		(χ trend = −0.85, p = 0.20)†	

* Androstenedione, testosterone, and estrone estimates adjusted for year of birth, and estradiol estimates adjusted for year of birth and history of prior use of exogenous hormones.

† p value for one-tailed test. Analysis excludes unknowns.

duction. The radiation dose to the adrenal glands would have averaged over 200 rads (16), a level which might have been sufficient to disrupt hormone production. Both androstenedione and testosterone are produced by the adrenal glands, and the major source of estrogens in menopausal women is from the peripheral conversion of androstenedione in adipose tissue (17).

Several limitations in this study should be noted. First, levels of the four hormones in the study population fell within normal ranges reported in the literature (18), but were on the low end of these ranges. The hormone assays had a fair amount (7–36 per cent) of variation at low levels, which may have prohibited detection of differences between the irradiated and the nonirradiated groups. In addition, the number of subjects in our study may have been too small to provide sufficient statistical power to detect small differences in hormone levels.

Second, the cross-sectional design of the study limited the evaluation of a woman's hormonal profile to one point in time, occurring an average of 20 years after treatment for cervical cancer. For a more complete answer to the study question, it would have been helpful to have pretreatment and multiple posttreatment hormone levels in irradiated and nonirradiated cervical cancer cases.

Third, the study participants were long-term survivors and thus a select group that may not be representative of the larger cervical cancer cohort. At the time of this study, 52 per cent of the original cohort

was deceased, including 61 per cent of the breast cancer cases. However, the protection against breast cancer in the cohort study appeared to continue irrespective of time since irradiation, which suggests that the study of long-term survivors might be of value.

Finally, the differences in hormone levels observed in this study did not reach the level of statistical significance and may be due solely to chance.

In conclusion, the differences in risk of breast cancer between irradiated and non-irradiated cervical cancer cases may be due to differences in hormone levels as a result of their treatment. The results of the trend analyses in this study suggest that irradiated women may have lower levels of androstenedione, testosterone, and estrone, possibly related to the effect of radiation on adrenal hormone production. While there was consistency in the trends for three of the four hormones and a biologically plausible explanation for these findings, the interpretation is made cautiously since the results were not statistically significant. It would be valuable to repeat this study in a larger population to see if these observations could be replicated.

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